REMARKS

The Invention

The invention features nucleic acids encoding attractin polypeptides and fusion proteins containing attractin polypeptides, vectors containing the nucleic acids, cells containing the vectors, and methods of making the polypeptides and the fusion proteins.

Status of the claims

Claims 1-46 are pending and claims 1-3, 6, 20-27, and 38-46 are under consideration in this application, claims 4-5, 7-19, and 28-37 having been withdrawn from consideration on the grounds that they are allegedly drawn to separate inventions. Claims 1-3 and 38-40 are allowed. The Office Action Summary (paragraph 6) indicates that claims 20-23, as well as claims 24-27 and 41-46, are rejected. However, body of the Office Action sets forth no rejection of claims 20-23. Thus it seems likely that claims 20-23, in addition to claims 1-3 and 38-40, are allowed. Clarification of this issue is requested. The amendment to claim 46 is supported by the specification, e.g., at page 22, line 35, to page 23, line 18; and page 30, lines 7-32. Other, non-substantive amendments serve merely to enhance the clarity of some of the claims. None of the claim amendments adds new matter.

Once the nucleic acid claims under consideration have been held allowable, Applicants propose, pursuant to 37 C.F.R. §1.121, to rejoin claims directed to methods of using the nucleic acid that are currently pending in the application and to request entry of suitable new method of use claims. Relevant pending "method of use" claims include, for example, claims 10 and 32.

35 U.S.C. §112, second paragraph, rejection

Claims 44-45 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

Applicants inadvertently recited in claims 44 and 45 the sequence identifier for the nucleotide sequence encoding membrane attractin-2 (SEQ ID NO:13) rather than the sequence identifier for the amino acid sequence of membrane attractin-2 (SEQ ID NO:12). Applicants

have corrected this error. The relevant amendment, which is supported by the specification (e.g., at page 20, lines 1-8), adds no new matter.

Applicants submit that, in light of the above amendment, the comments on page 2, paragraph 7, of the Office Action are moot and thus request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

35 U.S.C. §112, first paragraph, rejection for lack of enablement

Claims 6, 24-27, and 41-46 stand rejected on the grounds that the specification allegedly does not enable any person skilled in the art to which pertains to make and use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

From the comments on page 5, line 25, to page 4, line 12, of the Office Action, Applicants understand the Examiner to be taking the following positions: (i) it would require undue experimentation by one skilled in the art to make and use the nucleic acid (of claim 6) encoding a fusion because of the large number of functional fragments of SEQ ID NO: 12 that could be used in the first domains of such proteins; and (ii) it would take undue experimentation by one skilled in the art to make and use the DNAs of claims 41-45 in view of the large number of DNA molecules that have the specified levels of identity to the reference DNA, or that encode proteins having the specified levels of identity to the reference protein.

The Examiner's positions (i) and (ii) are addressed separately below.

Position (i)

The Examiner was not persuaded by Applicants' argument in the Response submitted April 30, 2003, that, while the three proteins (i.e., those with SEQ ID NOs: 2, 10, and 18) disclosed in the present specification are not strictly fragments of the protein with SEQ ID NO:12, they are informative with respect to enablement of such fragments. The Examiner apparently objects on the grounds that three species of a genus are not sufficient to enable the genus of functional fragments specified by claim 6 (page 4, lines 5-12, of the Office Action). Applicants are not aware of any "bright line" rule establishing the number of members of a genus

disclosed in a specification that is required in order to establish enablement of the genus, and certainly are not aware that this number has been established as something greater than three. Moreover, the Office Action does not indicate what number would be acceptable. Applicants submit that one of skill in the art would know, from the teaching of the specification in regard to making (e.g., at page 24, line 14, to page 26, line 21; page 39, line 5, to page 40, line 8; and page 49, line 5, to page 51, line 2) and using (e.g., at page 26, line 23, to page 34, line 32; and Examples 2, 5, 6, and 10) the three proteins having SEQ ID NOs:2, 10 and 18, and from the art, how to make and use the genus of functional fragments specified by claim 6. The Examiner is reminded that:

> a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable guidance with respect to the direction in which experimentation should proceed. *In re Wands*, 858 F.2d 731, 736-7 (Fed. Cir. 1988)

The Examiner has not explained why the guidance in the specification is not reasonable, nor why any needed experimentation would not be routine. In light of the above considerations, Applicants respectfully submit that the genus of functional fragment specified by claim 6 is enabled by the specification.

Position (ii)

In an apparent reference to the claims that specify a given level of sequence identity to either SEQ ID NO:12 or 13 (i.e., claims 41-45), the Examiner indicates at page 3 of the Office Action that the specification provides insufficient guidance as to what parts of the specified SEQ ID NO can be changed such that the resulting polypeptide encodes a protein with the required biological activity, i.e., the ability to enhance spreading of a macrophage or a monocyte. The Examiner cites references such as Attwood (Science 2000, 290:471-473) and Skolnick et al. (Trends in Biotech. 2000, 13:34-39) for the notion that assigning functional activities based on sequence homology is unpredictable. Applicants submit that this line of argument has no relevance to the present situation. The cited articles were addressing the problem of guessing the biological activity of proteins encoded by newly discovered genes where nothing is known about

the gene except that it shares some degree of homology with some previously studied gene—perhaps only within some small region of the gene. That is not the issue in the present case. One of ordinary skill in the art need not resort to comparing all random genes in any given genome to SEQ ID NO:13 and guessing that if some homology is shared with SEQ ID NO:13, it might encode a protein with the desired activity. Rather, if one of ordinary skill wished to find variants with 85% or 95% or 98% identity to SEQ ID NO:13 or 12, it is a simple matter to change one or two or more codons and test the encoded polypeptide. Furthermore, given the high degree of sequence identity required by these claims, it is highly likely that most of the polypeptides that have this high degree of identity will possess the desired activity. While it is certainly possible to abolish the activity of some proteins with a single amino acid change (as pointed out by the Examiner), most of such changes have little or no effect on biological activity. One of ordinary skill in the art would have no trouble finding species that fall within the claims. As the Examiner is aware, the question is not whether it is possible to find polypeptides that don't fall within the claims, but rather whether it would require undue experimentation to find some that do.

Applicants have disclosed how to make (see specification at, e.g., page 24, line 14, to page 26, line 21; page 39, line 5, to page 40, line 8; and page 49, line 5, to page 51, line 2) and use (e.g., see specification at, e.g., page 26, line 23, to page 34, line 32; and Examples 2, 5, 6, and 10) three species that fall within the scope of claims 41 and 43. These three sequences are SEQ ID NO:13 itself and two variants of SEQ ID NO:13 (i.e., SEQ ID NO:11 and SEQ ID NO:19) that lack either the transmembrane domain-encoding segment of SEQ ID NO:13 or a segment of 222 nucleotides in the 5' region of SEQ ID NO:13 (see, e.g., Examples 8 and 9).

Thus, in addition to the splice variant cDNA SEQ ID NO:13 (encoding SEQ ID NO:12), the specification discloses splice variant cDNAs with SEQ ID NOs: 1, 11, and 19 (encoding proteins with SEQ ID NOs: 2, 10, and 18, respectively). BLAST analyses performed as described on page 20, line 28, to page 21, line 10, of the specification indicate that SEQ ID NO:11 is 94.9%, SEQ ID NO:19 is 88.6%, and SEQ ID NO: 1 is 83.5% identical to SEQ ID NO:13. The computer printout of these analyses is enclosed as Exhibit A. In the first analysis,

SEQ ID NO:13 is compared to SEQ ID NO:19 ("secreted attractin (long 5' end)"), in the second analysis SEQ ID NO:12 is compared to SEQ ID NO:1 (secreted attractin (short 5' end)"), and in the third analysis SEQ ID NO:13 is compared to SEQ ID NO:11 ("membrane attractin (short 5' end)"; actual alignment not shown). The splice variants with SEQ ID NOs: 11, 13, and 19 fall within the range of levels of identity ("at least 85%") specified by claim 41. The variant with SEQ ID NO:13 falls within the higher range of levels of identity ("at least 95%") specified by claim 42 while that with SEQ ID NO:11 is only 0.1% outside of this range.

Applicants submit that from the teaching by the specification of how to make and use the DNAs with SEQ ID NOs: 11, 13, and 19, and the art, one of skill in the art would know, without undue experimentation, how to make and use species falling with scope of claims 41 and 42. Moreover, while another DNA analyzed by sequence alignment as described above (i.e., SEQ ID NO:1) falls outside the ranges of claims 41 and 42, the fact that it is even less similar to the reference sequence than the sequences that are within the specified ranges, but nevertheless has the requisite function (see, e.g., Examples 2 and 5 of the specification), provides additional support for the argument that the genera covered by claims 41 and 42 are enabled by the specification.

With respect to claims 43-45, the splice variant cDNA-encoded proteins with SEQ ID NO:10 (encoded by the cDNA with SEQ ID NO:11), SEQ ID NO:18 (encoded by the cDNA with SEQ ID NO:19), and SEQ ID NO:2 (encoded by the cDNA with SEQ ID NO:1) have been found by BLAST analyses performed as described on page 20, line 28, to page 21, line 10, of the specification to be 94.8%, 88.7%, and 83.6%, respectively, identical to the protein with SEQ ID NO:12. The computer printout of these analyses is enclosed as Exhibit B. In the first analysis, SEQ ID NO:12 is compared to SEQ ID NO:18 ("secreted attractin long form"), in the second analysis SEQ ID NO:12 is compared to SEQ ID NO:2 (secreted attractin short form"), and in the third analysis SEQ ID NO:12 is compared to SEQ ID NO:10 ("membrane attractin short form"; actual alignment not shown). Thus, the splice variants with SEQ ID NOs: 11, 13, and 19 fall within the range of levels ("at least 85%") specified by claim 43. The variant with SEQ ID NO:13 falls within the higher ranges of levels ("at least 95%" and "at least 98%") of identity

specified by claims 44 and 45, respectively, and that with SEQ ID NO:11 is only 0.2% outside of the range specified by claim 44. Moreover, one of these cDNAs (SEQ ID NO:1) encodes a protein that, even though it is even less similar to the reference protein than the proteins that are within the ranges specified by claims 43-45, has the requisite function (see, e.g., Examples 2 and 5 of the specification).

These findings, for reasons analogous to those presented above in regard to enablement of claims 41 and 42, indicate that the specification provides adequate enablement for claims 43-45.

35 U.S.C. §112, first paragraph, rejection for lack of written description

Claims 6, 24-27, and 41-46 stand rejected on the grounds that they allegedly contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Regarding claim 6 (and claims 24-27 and 46, which depend from claim 6), the Office Action says that Applicant is not in possession of any isolated nucleic acid encoding a fusion protein comprising a first domain and a second domain, wherein the first domain comprises an amino acid sequence consisting of SEQ ID NO:12 or any "functional fragment" of the amino acid sequence and wherein the second domain comprises any "heterologous sequence". No further elaboration of the rationale for this rejection is provided, other than a general statement that the skilled artisan cannot envision all the contemplated nucleic acid sequence possibilities recited in the claim. Thus, Applicants are uncertain as to the basis for the rejection. Certainly it cannot be the inability to envision everything contemplated by "heterologous sequence". One need simply envision any sequence other than what would normally occur in the relevant part of SEQ ID NO:12 in order to envision an "heterologous sequence." The specification lists various heterologous sequences that can be used to make the fusion proteins encoded by the DNA of claim 6, e.g., any of a variety of recited reporter polypeptides, immunoglobulin constant regions, and any of a variety of recited signal peptides (see, for example, page 22, line 35, to page 23,

line 18; and page 30, lines 7-32). Nor does the rejection seem likely to stem from the term "fragment" of SEQ ID NO:12, as one need only look at a printout of SEQ ID NO:12 in order to envision every possible fragment thereof. If the issue is the narrower term "functional fragment," Applicants note that considerable disclosure of functional fragments is provided in the specification, as discussed above with respect to the lack of enablement rejection—certainly sufficient written description to satisfy the requirements of U.S. law as elaborated by the courts. In the Response submitted April 30, 2003, Applicants pointed out that, while the three proteins (i.e., those with SEQ ID NOs: 2, 10, and 18) disclosed in the present specification were not strictly fragments of the protein with SEQ ID NO:12, they are informative with respect to such fragments. The Examiner argues that three sequences are not sufficient to support the genus of functional fragments specified by claim 6 (page 5, lines 17-26, of the Office Action). No authority is given for this conclusion. The Examiner does cite *Regents of the University of California v. Eli Lilly and Co.*, 199 F.3d 1559 (Fed. Cir. 1997) ("*Lilly*"), a case in which disclosure of one specie provided no guidance whatsoever as to the structure of other species within the claim, and so was held to be inadequate written description of the genus. The present case has facts markedly different from the *Lilly* case. For example, the structure of every "functional fragment" of claim 6 must be a subset of SEQ ID NO:12, and thus is rigidly circumscribed; in contrast, the specification in *Lilly* provided no clue to the structures of the molecules encompassed by the claimed genus of cDNAs, other than the rat cDNA sequence. The present specification discloses the function of SEQ ID NO:12 and provides the sequence of several splice variants that also possess the function. One of ordinary skill, reading the specification, could picture immediately a multitude of other species that would be expected to be "functional fragments" of SEQ ID NO:12, simply by virtue of containing most of SEQ ID NO:12. Applicants submit that one of skill in the art would understand from the teaching of the specification that the inventors were, at the priority date of the instant application, in possession of the invention specified by claims 6, 24-27, and 46.

Regarding claims 41-45, which are percent identity claims, Applicants note that Example 14 of the Written Description Guidelines states that a claim written in terms of percent

identity and containing a functional limitation does satisfy the written description requirement. Indeed, Applicants have an even stronger case than illustrated in this example in the Guidelines, in that the present specification discloses three species that fall within the scope of each of claims 41 and 43 (see above description of the sequence alignments). Applicants submit that the species disclosed are sufficient to convince one of ordinary skill in the art that the inventors were, at the priority date of the instant application, in possession of the invention specified by claims 41-45. If the Examiner intends to maintain the rejection, Applicants respectfully request that the rationale for the rejection be more fully explained, particularly in view of the above arguments and the Written Description Guidelines.

In light of the above considerations, Applicants request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed above.

Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 00530-089002.

Respectfully submitted,

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